KERATOCONJUNCTIVITIS SICCA DUE TO SARCOIDOSIS*

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SARCOIDOSIS is well recognized as a cause of swelling of the lacrimal glands and enters into the differential diagnosis of tumours of this region (Duke-Elder, 1952). Such swellings may be followed, in some cases, by a form of keratoconjunctivitis sicca (Ainslie and James, 1956; Gruber, 1956).

The association of systemic sarcoidosis with keratoconjunctivitis sicca in the absence of swelling of the lacrimal glands has also been described (Ainslie and James, 1956; James, 1956; Ramage and Kinnear, 1956), but in these cases the histology of the ocular lesions was not obtained; it was presumed, however, that they were of the same pathology.

In the case to be described, a patient, who had been treated in an ophthalmic clinic for 3 years for symptoms of conjunctival irritation, was found on mass radiography of the chest to have the typical radiological features of sarcoidosis. In view of this finding the patient was referred, after proof of systemic sarcoidosis had been obtained by liver biopsy, for investigation of her ocular condition. The patient's eyes lacked the generally accepted features of ocular sarcoidosis, namely swelling of the lacrimal glands, yellowish conjunctival follicles (Crick, Hoyle, and Mather, 1955; Crick, 1956), or chronic uveitis, but presented the clinical features of keratoconjunctivitis sicca. In addition she had complained of dryness of the nose and throat. Biopsy of lacrimal gland and conjunctiva, however, revealed that the ocular disorders were in fact due to sarcoidosis.

Case Report

A married woman aged 42, was admitted to The London Hospital for investigation in January, 1956. For 3 years she had complained of sticky threads forming in her eyes during the night. These were associated with a pricking sensation and discomfort which lessened during the day but worsened in the evening. For 3 years she had been treated for chronic conjunctivitis with a variety of drops, including penicillin and cortisone, without relief, and had been worsened by a course of silvering. She also noticed dryness of her nose and throat and would awaken with pharyngeal irritation and dryness, relieved by coughing up a tenacious plug of mucus.

For 2 years her chest had been under radiological observation since the discovery of hilar shadows and reticulation on mass radiography.

With the exception of intermittent pain in the right shoulder during the past 5 years,

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she had remained in good health until the onset of the ocular symptoms. Since then she had complained of lack of energy. She had one brother who died from tuberculosis.

**Examination.**—She was an athletic, well-nourished woman. Apart from the ocular features, the only abnormal finding was in the upper respiratory tract, where the nasal mucosa was relatively atrophic and rather dry. The mouth, larynx, and pharynx were normal. No abnormality of the skin, nails, salivary glands, lymphatic glands, or joints was discovered. The respiratory and cardio-vascular systems were clinically normal; blood pressure 130/90. The liver and spleen were not palpable and no abnormality was evident in the nervous system.

**Laboratory Investigations**

*Chest x-Ray.*—Diffuse infiltration in the lung fields especially in the upper lobes. Marked enlargement of the hilar lymph glands.

*Sputum and Gastric Lavage.*—No tubercle bacilli on smear or culture.

*Mantoux Test.*—Negative to 1 in 100 old tuberculin.

*Erythrocyte Sedimentation Rate.*—15 mm. in one hour.


*Haemoglobin.*—13·9 g. 100 ml.

*Liver Biopsy* (Fig. 1).—Needle biopsy showed non-caseous epithelioid cell tubercles with early peripheral fibrosis, morphologically compatible with sarcoidosis. No acid-fast bacilli.

**Ocular Examination.**—The lids were normal but the palpebral conjunctiva showed a mild degree of chronic injection. There was a tenacious string of mucus in each lower fornix. A band of slight subepithelial infiltration stretched across each lower fornix (Fig. 2, opposite). This was thicker and yellowish in some areas and there were other slightly infiltrated areas, but the condition could hardly be regarded as follicular. The bulbar conjunctiva was normal in appearance apart from rather prominent yellowish pingeuculae. Bengal rose stained the interpalpebral conjunctiva of each eye intensely
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Fig. 2.—Right eye showing minimal subepithelial infiltration in lower fornix but none of the yellowish follicles usual in conjunctival sarcoidosis. (Fig. 3), and with the Schirmer test only five mm. were wetted in 15 minutes in each eye. There was punctate staining of the lower third of each cornea with fluorescein or Bengal rose, but otherwise the globes were normal. Neither lacrimal gland could be palpated.

Fig. 3.—Left eye showing Bengal rose staining the interpalpebral conjunctiva.

Ocular Investigations.—No bacteria grew on conjunctival culture. Giemsa-stained conjunctival scrapings revealed no organisms and no virus inclusions in the epithelial cells. A scanty lymphocytic exudate was present and many of the epithelial cells showed the pink granulation of early keratinization.
Conjunctival biopsies from the infiltrated areas of each lower fornix and the left upper fornix were fixed in Zenker's fluid and stained with haemotoxylin and eosin. They showed an increased number of goblet cells and a slight subepithelial infiltration with lymphocytes and plasma cells (Figs 4 and 5).

Fig. 4.—Subepithelial granuloma in conjunctiva from right lower fornix showing epithelioid cells without caseation surrounded by lymphocytes. Haematoxylin and eosin × 150.

Fig. 5.—A giant cell accompanies the epithelioid cells in a non-caseating granuloma in conjunctiva of the left lower fornix. Haematoxylin and eosin × 330.
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Small scattered subepithelial granulomata consisting of large eosinophilic epithelioid cells surrounded by small lymphocytes were seen, and giant cells of the Langhans type were present in several. No acid-fast bacteria could be demonstrated.

A biopsy of the lower pole of the left lacrimal gland (Fig. 6) showed a diffuse increase in the interstitial lymphoid tissue with large aggregations of epithelioid cells without caseation, in which no tubercle bacilli could be seen.

Fig. 6.—Lower pole of left lacrimal gland with overlying conjunctiva. Sheets of non-caseating epithelioid cells and a diffuse increase in the interstitial lymphoid tissue have largely disorganized this lobule. Haematoxylin and eosin × 53.

Treatment.—She was given cortisone 100 mg. daily orally, reduced after 3 months to 75 mg. daily, together with Isoniazid 300 mg. daily and para-aminosalicylic acid 3·5 mg. four times daily. She is continuing this treatment at the time of writing. There has been marked symptomatic improvement.

Discussion

Clinically this patient presented with the features of keratoconjunctivitis sicca and not those characteristic of ocular sarcoidosis. Moreover, the keratoconjunctivitis was associated with dryness of the nasopharynx, features more in keeping with Sjögren’s syndrome. It was only when evidence of pulmonary sarcoidosis was brought to light that the possibility of a similar aetiology of the ocular condition was considered.
Sjögren's Syndrome.—Sjögren and many others (reviewed by Duke-Elder, 1952) have emphasized that keratoconjunctivitis most often arises without preceding ocular disease in middle-aged women and is often associated with polyarthritis, xerostomia, salivary gland enlargement, and rhinitis, pharyngitis and laryngitis sicca. Many other abnormalities have been recorded in patients with dry eyes (Duke-Elder, 1952) and added to the syndrome; in many cases the syndrome is incomplete. There is an unfortunate tendency for keratoconjunctivitis sicca and almost any associated feature to be diagnosed as “Sjögren’s disease” without further systemic investigation or treatment.

Nature of Sjögren’s Syndrome.—There are four main views of this syndrome. Firstly, it has been regarded as a disease in its own right which gives rise to some or many of the possible clinical features (Sjögren, 1933; Henderson, 1950; Coverdale, 1948, 1952; Cardell, and Gurling, 1954).

Secondly, the syndrome has been regarded as a manifestation or complication of rheumatoid arthritis. Thompson and Eadie (1956) recently supported this view by an extensive investigation of patients with rheumatoid arthritis, in which they established that keratoconjunctivitis sicca is the commonest ocular complication of rheumatoid arthritis. However, rheumatoid arthritis cannot be the aetiology of those fairly common cases of Sjögren’s syndrome without arthritis unless they represent anarthritic rheumatoid disease (Bagratuni, 1956).

Thirdly, since keratoconjunctivitis sicca has been described in association with several collagen diseases other than rheumatoid arthritis, namely, rheumatic fever, polyarteritis nodosa, disseminated lupus erythematosus, and scleroderma, it has been suggested that Sjögren’s syndrome is merely one variant of collagen disease (Ramage and Kinnear, 1956; British Medical Journal Editorial, 1956).

Fourthly, the syndrome may be regarded as a syndrome and no more, that is to say a symptom complex which may arise from a variety of pathological processes. Having recognized the syndrome in any particular case, we should attempt to make an aetiological diagnosis. Thorough systemic examination may establish the presence of one of the collagen diseases. It is at this point that sarcoidosis should also be considered, and the patient carefully investigated for systemic and ocular sarcoidosis. The present case clearly demonstrates the simplicity and value of conjunctival and lacrimal biopsy in making the diagnosis and in establishing that the systemic disease and the ocular condition are in fact due to the same cause.

From among patients with keratoconjunctivitis sicca some will also be recognized who are presenting the early stages of a disease resembling ocular pemphigus.
Features of Sjögren’s Syndrome which can arise in Sarcoidosis.—The present case shows that keratoconjunctivitis sicca can result from lacrimal and conjunctival sarcoidosis even without swelling of the lacrimal gland, as described by Gruber (1956), or manifest conjunctival follicles as described by Crick and others (1955). Swelling of parotid and other salivary glands has been recorded in numerous cases of sarcoidosis (Longcope and Pierson, 1937; Pautrier, 1938; Scott, 1938; Schultz, 1945). Xerostomia would be expected in a patient whose salivary glands were infiltrated by sarcoïd deposits or disorganized by subsequent fibrosis (James, 1956). The present patient also had symptoms of rhinitis and pharyngitis sicca and the nasal mucosa had a dry and somewhat atrophic appearance. Infiltration of the nasal, paranasal, pharyngeal, and laryngeal mucosa in sarcoid have been demonstrated (Poe, 1942; Bordley and Proctor, 1942; Wille, 1946). Enlarged superficial lymph nodes, spleen, and liver are all well-recognized occurrences in sarcoidosis. Like other possible features of Sjögren’s syndrome, their significance varies with the presence or absence of arthritis. If a patient with keratoconjunctivitis sicca has rheumatoid arthritis and enlargement of lymph nodes and spleen, then she is probably presenting Felty’s syndrome. If she has no arthritis then sarcoidosis is more likely. Mild pyrexia, raised erythrocyte sedimentation rate, and hyperglobulinaemia not uncommonly occur in sarcoidosis and are often found in cases of Sjögren’s syndrome associated with rheumatoid arthritis.

Features of Sjögren’s Syndrome not expected to arise from Sarcoidosis.—Polyarthritis of the rheumatoid type does not result from sarcoidosis, so that the presence of definite rheumatoid arthritis in any case makes sarcoidosis much less likely. James, Thomson, and Willcox (1956) have recently drawn attention to the occurrence of an acute polyarthritis in association with the erythema nodosum which may arise in sarcoidosis and this must not be confused with a true rheumatoid arthritis. The dry brownish-yellow longitudinally fissured nails described by Thompson and Eadie (1956) similarly appear to be a feature in those cases of Sjögren’s syndrome associated with rheumatoid arthritis.

Summary

A case of keratoconjunctivitis sicca with symptoms of dryness at the back of the mouth was shown by biopsy to be due to lacrimal and conjunctival sarcoidosis. Systemic sarcoidosis was demonstrated by chest x-ray and liver biopsy.

The relationship of Sjögren’s syndrome to rheumatoid arthritis and to sarcoidosis is discussed, and it is suggested that general investigation, conjunctival biopsy and possibly lacrimal biopsy should be used to elucidate the aetiology in those patients who do not have a rheumatoid arthritis.
accompanying their dry eyes. If the keratoconjunctivitis sicca is accompanied by yellowish conjunctival follicles, swelling of the lacrimal glands, or chronic uveitis, then sarcoidosis is more likely. Although sarcoidosis may well account for only a small proportion of cases of keratoconjunctivitis sicca, these cases are worth recognizing since the disease is known to respond to cortisone and it is reasonable to suppose that if treatment can be maintained until it becomes inactive then permanent damage by fibrosis can be prevented.

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REFERENCES